

Sexual dimorphism in prophase I of meiosis in the Northern mole vole (*Ellobius talpinus* Pallas, 1770) with isomorphic (XX) chromosomes in males and females

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Abstract. The synaptonemal complex (SC) surface-spreading technique was used to visualize the process of chromosome synapsis in spermatocytes and oocytes of *E. talpinus* Pallas, 1770, a species with the XX sex chromosome system in both males and females. We used electron microscopy and immunofluorescent localization of synaptonemal complex protein (SCP3) and centromeric proteins to analyze the structure and behaviour of synaptonemal complexes in prophase I of meiosis, aiming to reveal signs of meiotic sexual dimorphism in this species. We present evidence of considerable differences in the structure and behaviour of the axial structures of sex bivalents in male and female meiosis, despite the isomorphic G- and C-banding patterns of mitotic sex chromosomes. During meiotic prophase I, the sex bivalent in females behaved as autosomal bivalents, but it was not involved in the formation of the bouquet configuration or it was the first to leave it. The XX chromosomes of males formed closed sex bivalents. Only short tracts of SC were formed at both ends of the sex bivalent, while large middle segments of the lateral elements remained unpaired. The male sex chromosomes also formed characteristic “sex bodies”. In fact, electron microscopy revealed dense nucleolus-like bodies associated with unpaired parts of the axial elements. These regions of the sex chromosomes were poorly immunostained, because the distribution of SCP3 had a peculiar powder-like pattern, but SCP3 was not associated with the nucleolus-like bodies. We also revealed signs of sexual dimorphism in the dynamics of formation and destruction of autosomal SCs. In males, the total SC length was shorter than in females. The chromosome bouquet configuration was preserved up to the stage of early pachytene in females. The bouquet configuration in males was not expressed. At late pachytene, gaps were revealed in the structure of autosomal SCs in spermatocytes immunostained with antibodies to SCP3. The pattern of distribution of these gaps was comparable with the G-banding patterns of mitotic chromosomes.

Key words: sexual dimorphism, meiosis, synaptonemal complex, male isomorphic sex chromosomes, *Ellobius talpinus*, variable position of centromeres.

INTRODUCTION

The key point for evolution and development of sexually dimorphic organisms

is the production of genetically dissimilar gametes by meiotic division. The knowledge of sexual dimorphism in meiosis has been

considerably extended in recent years due to active interest in the problems of regulation in meiosis and the mechanisms of selection of meiotic cells, which are different in females and males (Forejt, 1984; Tease, Hultén, 2004; Morelli, Cohen, 2005).

Meiosis in males is an entirely postnatal event. Germ cells enter meiosis prior to puberty, and gametogenesis continues in waves throughout adult life recruiting a new population of germ cells to enter meiosis during each wave of spermatogenesis (Handel, Eppig, 1998).

Unlike males, female meiosis starts in the ovary in the foetal period. Prophase I is mostly completed during foetal development, and the oocytes then enter the dictyotene arrest. Later, the oocytes remain quiescent until female sexual maturation, when one or more oocytes are recruited in each oestrous cycle to resume meiosis. Therefore, the meiotic cell cycle in mammals is a process that includes several check points (Dyban, Baranov, 1977; Kurilo, Zelenin, 1985; Morelli, Cohen, 2005). Moreover, sexual dimorphism implies that the processes of recombination, chromosome pairing, synapsis, and desynapsis of homologous chromosomes are subjected to different levels of checkpoint control in males and females (Morelli, Cohen, 2005).

Sexual dimorphism represents one of the fundamental evolutionary challenges (Williams, Carroll, 2009). In mammals, it is determined by sex chromosome systems, commonly XX/XY. But this is only true for placentals and marsupials, the monotremes have multiple sex chromosomes (Veyrunes et al., 2008). Among placental mammals, only some rodent species show atypical sex chromosome systems. There are at least four types of deviations (Veyrunes et al., 2010): (1) typical XY males and different females with XX and XY in *Myopus schisticolor* Lilljeborg, 1844, *Dicrostonyx torquatus* Pallas, 1778,

Akodon sp. (Fredga, 1983, 1994; Hoekstra, Edwards 2000; Ortiz et al., 2009); (2) typical XY males and deviant XO females (single X) in *Microtus oregoni* Bachman, 1839 (Ohno et al., 1966; Fredga, 1983); (3) females and males with XO karyotypes in *Tokudaia osimensis* Abe, 1933, *T. tokunoshimensis* Endo et Tsuchiya, 2006 (Arakawa et al., 2002) and *Ellobius lutescens* Thomas, 1897 (Matthey 1953; Just et al., 1995); (4) males and females with identical isomorphic XX in three sibling species of *Ellobius*, *E. tancrei* Blasius, 1884, *E. talpinus* Pallas, 1770 and *E. alaicus* Vorontsov et al., 1969 (Vorontsov et al., 1980; Bakloushinskaya, Lyapunova, 1990; Just et al., 2007; Romanenko et al., 2007).

Differences in the structure and behaviour of sexual bivalents most vividly exemplify sexual dimorphism in prophase I of meiosis (Turner et al., 2000; Cohen et al., 2006; Handel, Eppig, 1998; Hayashi et al., 2000).

The behaviour of the sex chromosomes during prophase I is evidently different in mammalian males and females with heteromorphic sex chromosomes, even if some peculiar species-specific features are acknowledged, whereas the systems with XO and XX sex chromosomes, identical in females and males, are extremely interesting for understanding underlying events in the determination of sexual dimorphism in meiosis.

The genus *Ellobius* Fischer, 1814 represents a group of rodent species with a remarkable system of sex determination. Indeed, it shows three types of sex chromosomes: the common XX/XY in *E. fuscicapillus* Blyth, 1843, the XO/XO in *E. lutescens*, and the indistinguishable XX/XX in the group of sibling species, *E. talpinus*, *E. tancrei*, and *E. alaicus*. This latter system is unique among mammals, which gives a rare opportunity to investigate sex determination and necessity of X chromosome inactivation in males.

So far, we have studied male meiosis in three *Ellobius* species and revealed some species-specific traits of it (Kolomiets et al., 1991). As yet no comparative study of male and female meioses has been performed for *Ellobius*. Furthermore, because of the uncertain systematic status of two sibling species *E. talpinus* and *E. tancrei*, previously, we used the species name “*talpinus*” for *E. talpinus* sensu stricto and for different chromosomal forms of *E. tancrei* (Bogdanov et al., 1986). It is worth mentioning that the complicated situation in the taxonomy of *Ellobius* led to confused species descriptions in various reports including the last edition of the “Mammal species of the world” (Musser, Carleton, 2005). In spite of Topachevsky’s opinion (1965), the two species were not divided by taxonomists until additional morphological and chromosomal studies were carried out (Vorontsov, Yakimenko, 1984).

To investigate female meiosis, we have started the study with a chromosomally stable species, the Northern mole vole - *E. talpinus*. The karyotype of this species was described by Ivanov (1967) as $2n = 54$, $NF = 54$. The author failed to identify sex chromosomes, but hypothesized the typical, XX/XY, sex chromosome system. In *E. talpinus*, differences in the male and female chromosomal sets and, especially, in chromosomes defined as XX did not emerge after either G- banding or Zoo-FISH with X-chromosome probes of *Microtus agrestis* Linnaeus, 1761, *Mus musculus* Linnaeus, 1758, *Mesocricetus auratus* Waterhouse, 1839, human, and rat (Romanenko et al., 2007).

The study of meiotic features in *E. talpinus*, as a species with isomorphic XX chromosomes in both sexes, may further contribute to general understanding of the role and significance of sex dimorphism. The main goal of our study is to investigate meiotic behaviour of indistinguishable male and female sex

bivalents during prophase I.

MATERIAL AND METHODS

Animals. All *E. talpinus* specimens (three females and three males) were obtained from a laboratory collection of N. K. Koltzov Institute of Developmental Biology, Russian Academy of Sciences. Testes were obtained from mature (not younger than 1 year) males and ovaries from one-day-old females.

Coating of slides. Slides for a subsequent electron-microscopic study were covered with Falcon film. Slides coated with poly-L-lysine were used for immunostaining.

Preparation of cell suspension. The suspension of oocytes was prepared by our own method. Ovaries were removed and transferred onto a drop of Eagle’s medium (without glutamine) on the surface of a slide. The ovaries were overlaid with a cover slip. The cover slip was carefully pressed, under visual control, with a dissecting needle to separate the ovarian cells. The cover slip was lifted at one side, and the suspension of cells was collected and put into a centrifuge tube and then homogenized with an automatic pipette and placed on ice. The suspension of spermatocytes was left in a centrifuge tube and washed by centrifugation with 10 ml of Eagle’s medium, 2-3 times for 10 minutes at 1500 rpm. After that the tube with cells was placed on ice.

Cell spreading and fixation. Spreads were prepared and fixed using the technique of Navarro et al. (1981) with some modifications.

Electron microscopy. The slides were stained with 50% $AgNO_3$ solution in a humid chamber at 56°C for 3 hours. The slides were washed in four changes of distilled water and air-dried. The stained slides were observed in a light microscope, suitably spread cells were selected, and plastic (Falcon film) circles were

cut out with a diamond tap and transferred onto grids. The slides were examined under JEM 100B electron microscope.

Immunostaining. The slides were washed in PBS. Whole mount SCs were blocked with HB (holding buffer: PBS, 0.3% BSA, 0.005% Triton X-100). The slides were incubated overnight at 4°C with rabbit polyclonal antibodies against the human lateral element protein SCP3 (Abcam, 15093Ab, UK Cambridge, UK) diluted to a concentration of 1:200 in ADB (Antibody Dilution Buffer: PBS, 3% BSA, 0.05% Triton X-100) and with human anti-centromere antibodies, ACA, (Antibody Incorporated, California, USA) diluted to a concentration of 1:200 in ADB. The slides were washed in PBS and incubated with goat anti-rabbit Alexa Fluore 488 conjugated antibodies (1:800, Abcam, Cambridge, UK) and goat anti-human Alexa Fluore 546 conjugated antibodies (1:800) at 37°C for 60 min. The slides were washed with PBS, rinsed briefly with distilled water, dried and mounted in Vectashield with DAPI (Vector Laboratories).

The slides were analyzed with an Axioimager D1 microscope CHROMA filter sets (Carl Zeiss, Jena, Germany) equipped with an AxioCam HRm CCD camera (Carl Zeiss), and image-processing AxioVision Release 4.6.3. software (Carl Zeiss, Germany). Images were processed using Adobe Photoshop CS3 Extended.

Measurements of autosomal bivalents, in order to determine their relative lengths and their ranking in each cell, were made with MicroMeasure 3.3 (Colorado, USA) using the STATISTICA 8.0 (StatSoft, Inc., 2008).

RESULTS

Female SCs. On the first day after birth, the females of *E. talpinus* present oocytes at different stages of prophase I, from

preleptotene to diplotene. At preleptotene, when the formation of axial elements just begins, and homologous chromosomes are not coupled yet, foci immunostained with ACA are scattered over the whole nucleus, and only single centromeres are joined in pairs or pulled together (Fig. 1, a).

At early zygotene, the telomeres are grouped close to one pole of the nucleus. As *E. talpinus* has only acrocentric chromosomes, the immunolabeled centromere-telomere chromosome ends are visualized most clearly (Fig. 1, b). The chromosome bouquet configuration is retained in oocytes at the stage of early pachytene (Fig. 1, c). In the immunocytochemical analysis, oocytes with completely formed SCs were detected at the stage of middle pachytene (Fig. 1, d).

As a rule, one large ACA signal was observed on one SC, but two signals were revealed in single SCs, since the positions of the centromeres on homologous chromosomes did not coincide (Fig 1, c-e). Different lengths of the short arms of acrocentric chromosomes of different SCs are worth noting.

At diplotene, desynapsis of homologous chromosomes begins at the telomeric ends in some SCs and, in other SCs, in the interstitial regions of bivalents (Fig. 1 f).

In electron microscopic analysis, no oocytes had completely formed SCs in all chromosomes in concert. At the pachytene, several chromosomes, in which interstitial regions of homologous chromosomes remained asynaptic, were constantly detected. Nonhomologous synapsis of chromosomes was not observed at all (Fig. 2) in either stage of prophase I of meiosis.

Both immunostaining and electron-microscopic methods did not allow discrimination between the sex bivalent and autosomes. To identify the XX bivalent in oocytes, we compared the relative lengths of

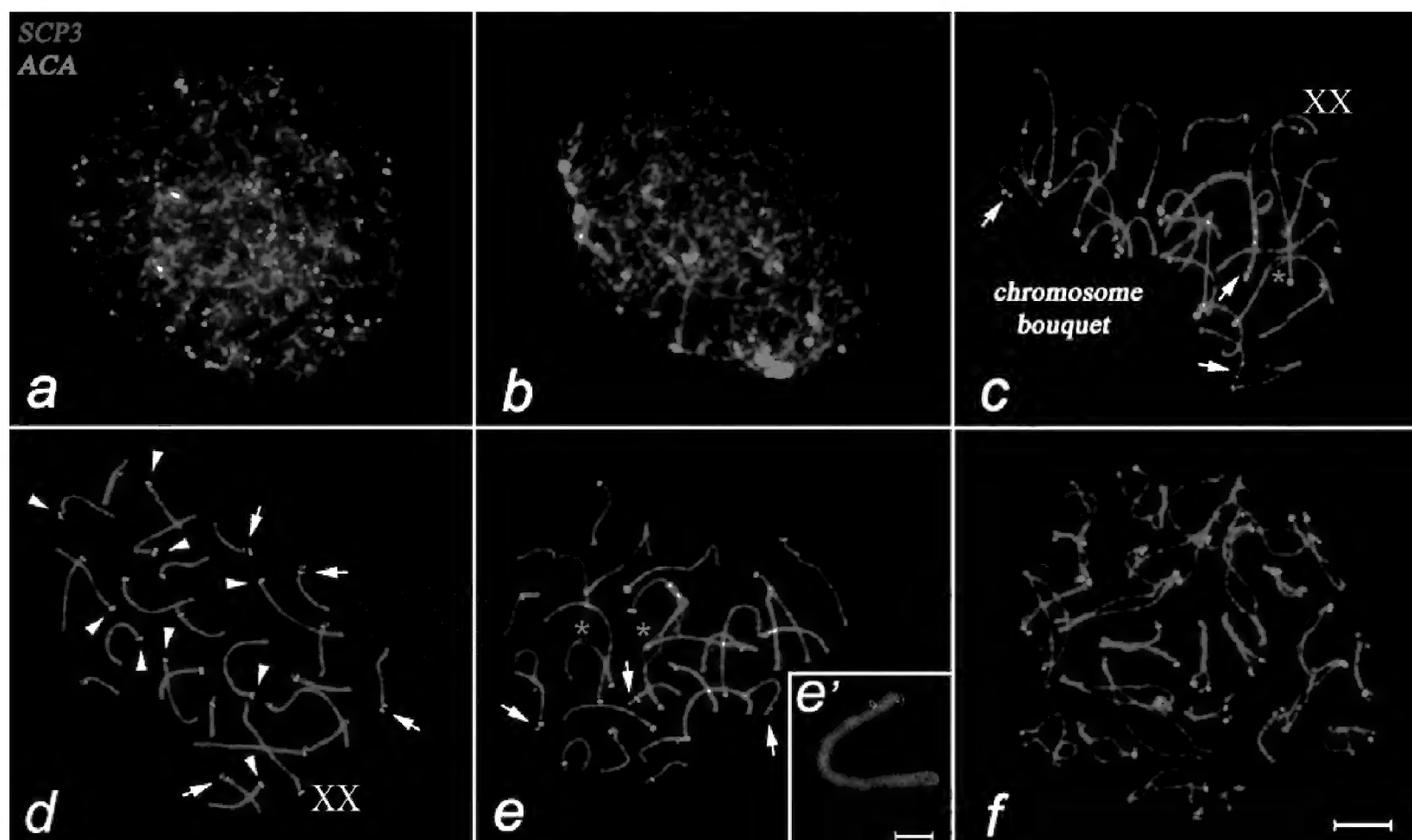


Fig. 1, a-f. Spreads from *E. talpinus* oocytes immunolabeled with antibodies to the centromere (red) and SCP3 (green). **a** - preleptotene. Centromeres (red) are scattered over the nucleus. Only short fragments of the axial elements (green) have been formed. **b** - early zygotene. The formation of the axial elements and bouquet configuration is visible. **c** - Early pachytene. All 27 SCs have already been formed. Most SCs are in the bouquet configuration, except sex bivalent (XX). **d** - middle pachytene. Two ACA signals lie on distance from each other on four SCs (arrows). Short arms of some chromosomes are not visible (arrow heads). **e** - early diplotene. Two ACA signals lie on distance from each other on three SCs (arrows). Asynaptic zone of two SCs are visible (snowflake). **e'** - two signals of the ACA on SC lie on distance from each other. Bar=1 μ m. **f** - middle diplotene. Desynapsis of chromosomes begins in the telomeric ends and in the interstitial regions of bivalents. Immunolabeling of SCs with antibodies to SCP3 has the banding pattern. Bar = 3 μ m.

metaphase chromosomes and bivalents (Fig. 3). We noticed that at the stage of pachytene the sex bivalent is one of the first to become straight and leave the bouquet configuration (Fig. 1, c). The total synaptonemal complex complement length at pachytene in oocytes is $155 \pm 7 \mu$ m.

Male SCs. In spermatocytes, the total SC length at pachytene is $119 \pm 11 \mu$ m. The bouquet configuration of chromosomes in spermatocytes is not expressed. Beginning from zygotene, the sex bivalent is located in the nucleus periphery; the axial elements are surrounded by a cloud of electron-dense

material. The XX chromosomes form a closed bivalent with two short paratelomeric SC fragments. In the central part of the sex bivalent, the thin axial elements of XX chromosomes do not approach each other, but are repulsed from one another. An electron-dense nucleolus-like body is formed on one of the axial elements (Fig. 4, a). During the progression of prophase I of meiosis, twisting of the sex chromosome axes occurs. The axial asynaptic regions intersect, short thorns are gradually formed on the axial elements, and a nucleolus-like body is also formed on the axial element of the second X chromosome

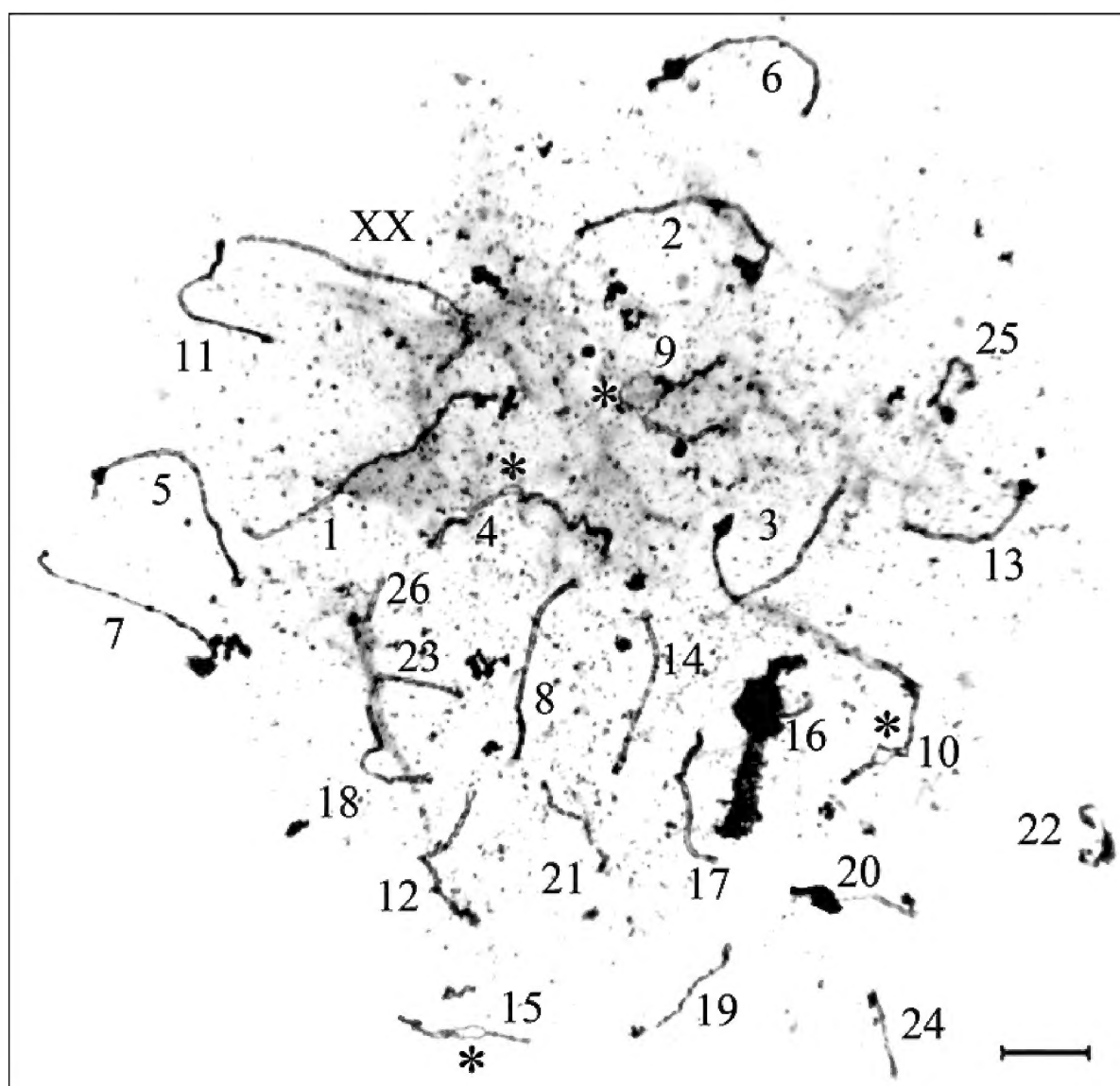


Fig. 2. Spread from an *E. talpinus* oocyte at early diplotene examined with transmission electron microscopy. Numbers of SCs correspond to numbers of metaphase chromosomes of *E. talpinus* (Romanenko et. al., 2007). Asynaptic zones of SCs are visible (snowflake). Bar = 3 μ m.

(Fig. 4, b). At the stage of diplotene, the cloud surrounding the bivalent becomes denser (Fig. 4, c).

Gaps in the structure of autosomal SCs were revealed at late pachytene-early diplotene in *E. talpinus* spermatocytes immunolabeled with antibodies to SPC3 (Figs 5, 6). The distribution pattern of the gaps is similar to G- and C- banding patterns of mitotic chromosomes (Fig. 6).

DISCUSSION

Autosomes. The present study revealed a number of differences in the structure and behaviour of autosomes in oocytes and spermatocytes of *E. talpinus*. First, the difference in the average total length of autosomes in

females and males is conspicuous. Based on the electron microscopy data, the total SC length at the stage of pachytene is greater in females ($155 \pm 7 \mu$ m) than in males ($119 \pm 11 \mu$ m). These data agree with the data of other authors. For example, the total length of the SC complement at pachytene in human female (519 μ m) is about twice the respective length in male (Wallace, Hulten, 1985). Accordingly, approximately 50 crossovers occur in one human spermatocyte, while there are 70 crossovers in one oocyte. In addition, the loop size is shorter in oocytes than in spermatocytes (Tease, Hulten, 2004). For that reason, meiotic chromosomes at the pachytene stage of meiosis I, when crossing-over takes place, should be packed in different ways in human

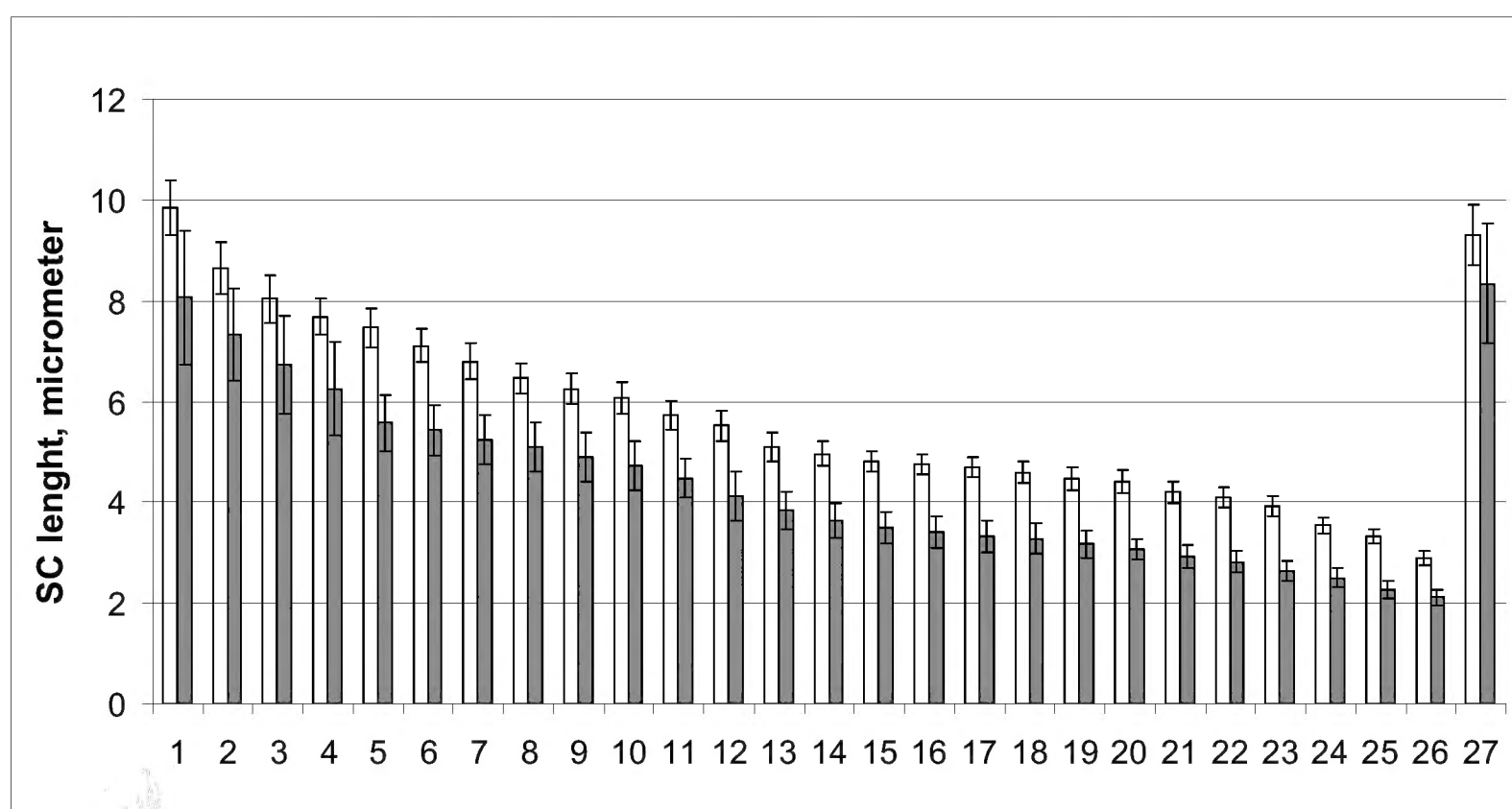


Fig. 3. The average relative length of SCs of oocytes (columns without fill) and spermatocytes (grey columns) of *E. talpinus* at pachytene. Numbers on the abscissa correspond to the length of autosomes; the 27 pair is the sex chromosomes (XX).

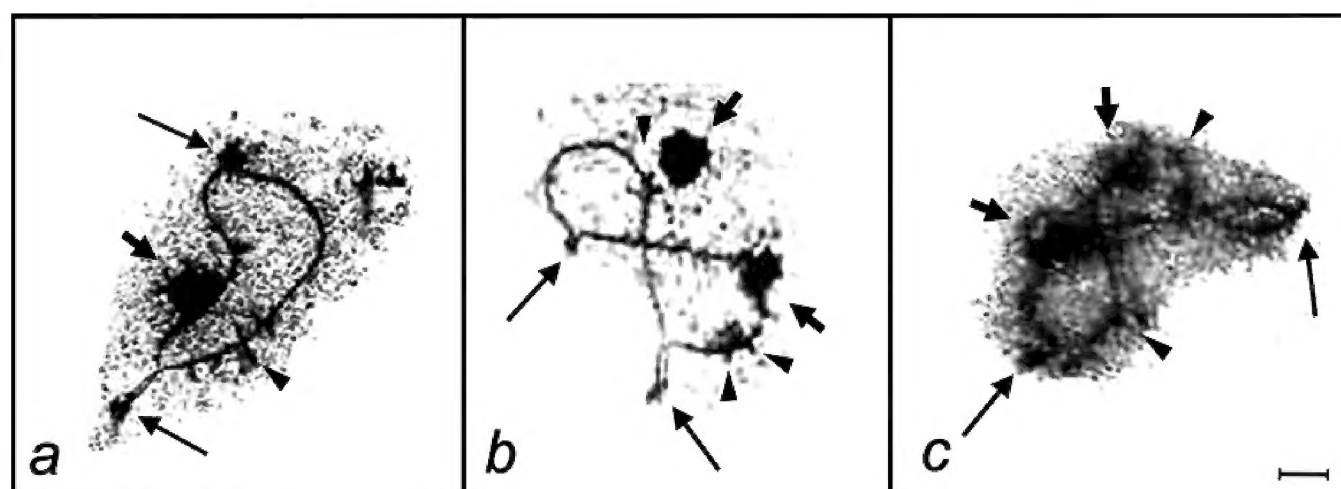


Fig. 4, a-c. Dynamics of the sex bivalent structure in *E. talpinus* spermatocytes in prophase I of meiosis. SCs spread from *E. talpinus* spermatocytes examined by transmission electron microscopy. The *arrowhead* indicates thorns on axes. The short *arrow* indicates the electron-dense nucleolus-like body; the *long arrows* indicate short paratelomeric SC fragments. Bar = 1 μ m. **a** - late zygotene. A closed sex bivalent with short paratelomeric SC fragments and extensive zone of asynapsis between the axial elements of XX chromosomes. **b** - pachytene. Two electron-dense nucleolus-like bodies at each of XX chromosomes axes. **c** - diplotene. The compact sex bivalent has a complicated configuration and is surrounded by a "cloud" of electron-dense material.

oocytes and spermatocytes (Wallace, Hulten, 1985; Tease, Hulten, 2004). This is thought to be determined by a special role of female sex cells, which implies not only transmission of

genetic information to the next generation, but also provides a the trophic function of a zygote after fertilization. This function is manifested in a high transcriptional activity of DNA of

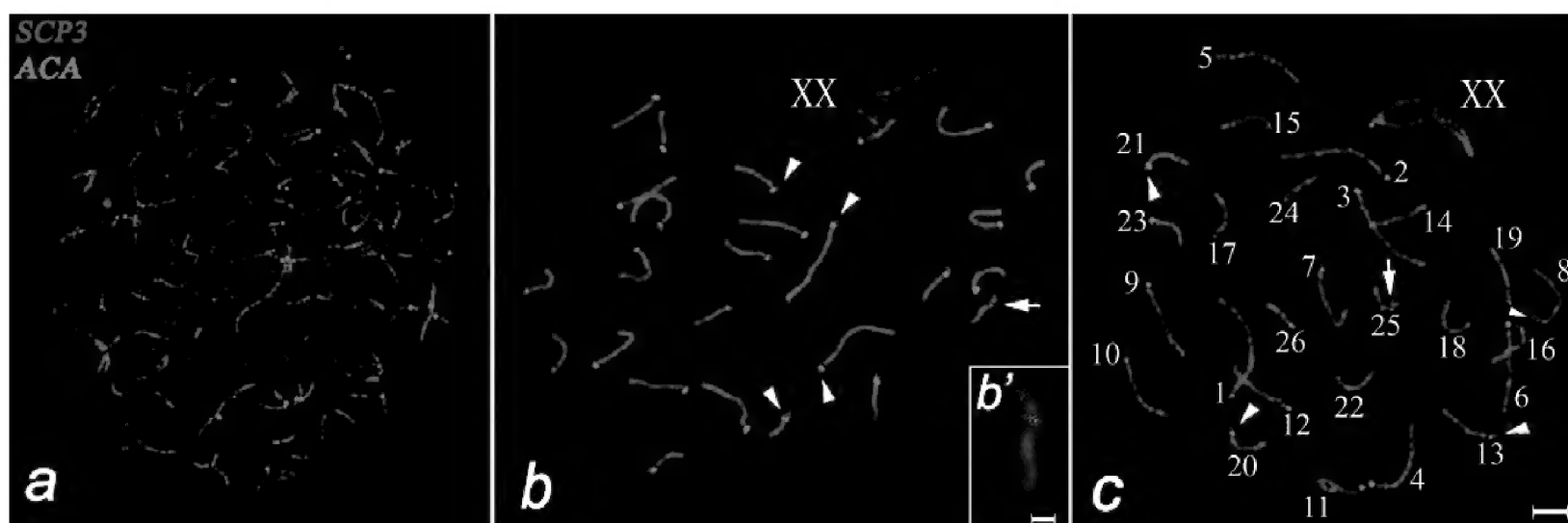


Fig. 5, a-c. Spreads from *E. talpinus* spermatocyte immunolabeled with antibodies to the SCP3 (green) and centromere (red; ACA) proteins at different stages of prophase I of meiosis. **a** - early zygotene. The formation of the axial elements without bouquet configuration is visible. **b** - middle pachytene. Autosomal SCs are uniformly stained; and the SCP3 distribution in the asynaptic regions of the sex bivalent (XX) axes has the powder-like pattern. Short arms of some chromosomes are visible (arrow heads). Signals of the ACA on one SC lie on distance from each other (arrow). **b'** - Short acrocentric SC with two ACA signals, which lie on distance from each other. Bar = 0.5 μ m. **c** - late pachytene. Banding pattern of the SCP3 protein distribution over autosomal SCs and a very weak SCP3 fluorescence signal on the sex bivalent axial elements. Numbers of SCs correspond to numbers of metaphase chromosomes *E. talpinus* according to Romanenko et al. (2007). Bar = 3 μ m.

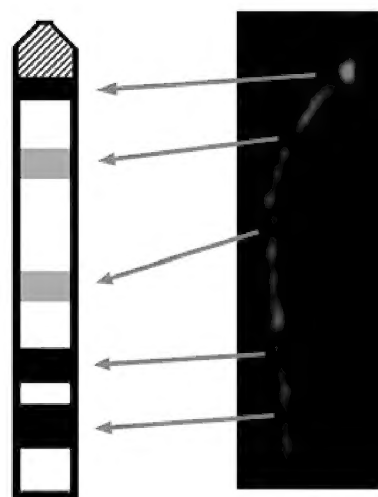


Fig. 6. Late pachytene. Comparison of the distributions of gaps in the SC for the second biggest bivalent and G-bands for the second biggest mitotic chromosomes (Romanenko et al., 2007).

meiotic chromosomes, which is associated with their lower level of condensation (Tease et al., 2002, 2006).

Second, our electron microscopic analysis in oocytes of *E. talpinus* failed to reveal SCs with completely paired lateral elements, although such oocytes were detected

immunocytochemically. On the contrary, full synapsis of autosomes at the stage of pachytene was always observed in spermatocytes. Accordingly, abnormal chromosome synapsis is observed in 30% of oocytes obtained from normal human fetuses. Univalents are formed in 15% of cells, and in 16% of cells chromosomes enter nonhomologous synapsis (Speed, 1986; Speed, Chandley, 1990). Actually, asynapsis and nonhomologous synapsis at the stage of pachytene in female meiosis occur much more frequently than in male meiosis (Ohno et al., 1963). Ohno et al. (1963) advanced a hypothesis, according to which the associations of nonhomologous chromosomes in prophase I of meiosis is the reason why oocytes remain blocked for a long time and thus do not enter metaphase I. It should be emphasized that we used females obtained on the first day after birth, while other authors, as a rule, examined foetal oocytes. We managed to obtain oocytes from the preleptotene stage to the stage of diplotene-dictyotene, including

oocytes with full chromosome synapsis at the pachytene (Fig. 1 d).

Third, differences in formation of the bouquet configuration by male and female chromosomes were noted.

These three instances of sexual dimorphism, regarding the structure and behaviour of chromosomes in meiosis, have been noted in numerous heterogametic mammalian species and humans (Wallace, Hulten, 1985).

Immunolabeling with antibodies to SCP3, the major protein of the axial elements of chromosomes, and centromere proteins revealed further differences between females and males in the processes of SC formation and destruction. Thus, the elimination of the SCP3 protein from spermatocyte SCs begins from the regions corresponding to G bands of mitotic chromosomes at late pachytene. This phenomenon in females of *E. talpinus* is observed only at diplotene (Fig. 4). Earlier this tendency has been established by us at research elimination SCP3 from SCs of *Mus musculus* and *Mesocricetus auratus*. In male rats this tendency has not been observed (Davtian, Kolomiets, 2008).

In accordance with the model of meiotic pairing proposed by Chandley, early replicating sites along chromosomes, corresponding to R-bands, are envisaged as sites for synaptic initiation. Only within these regions «effective» pairing for recombination is established. Interestingly, the signs of sexual dimorphism were noted in dynamics of SCs proteins and at more late stages of meiosis Chandley (1996).

According to literature data, the traces of SC proteins (SCP2, SCP3) disappear from chromosomes before the beginning of metaphase I in oocytes, which is one of the causes of PSCS (Precocious Sister Chromatid Segregation) and leads to an increased frequency of aneuploidy in female

gametes (Angell, 1997). In spermatocytes, the SC proteins remain closely associated with centromeres until anaphase II and hold sister chromatids together, providing correct segregation of chromosomes to the spindle poles. The authors, who described this phenomenon, considered it as manifestation of sexual dimorphism in meiosis (Hodges et al., 2001).

The discrepancy in positions of two ACA signals on SCs remains unclear. It may be either an intrinsic feature of SC proteins and their dynamics in meiosis or it is probably caused by variable position of centromeres in this species.

Sex chromosomes. Differences in the structure and behaviour of sex chromosomes in males and females represent particular interest, since strong evidence in favour of isomorphism for G-banding of XX chromosomes in *E. talpinus* males and females has been provided (Vorontsov et al., 1980; Bakloushinskaya, Lyapunova, 1990; Just et al., 2007; Romanenko et al., 2007). However, it is apparent from the results presented here that not only the structure of the sex bivalent, but also the dynamics of its behaviour in prophase I of meiosis in *E. talpinus* males, have features characteristic of representatives of the heterogametic sex carrying heteromorphic sex chromosomes. The feature most indicative of heteromorphism of XX chromosomes in *E. talpinus* males is the incomplete synapsis between them with an extensive zone of asynapsis in the central region of the sex bivalent.

The second and also convincing feature of «heteromorphism» of XX chromosomes in males of *E. talpinus* is the formation of a sex body in the nucleus periphery. It appears already at the stage of zygotene, whereas in mice the formation of a sex body is observed at middle-late pachytene (Forejt, 1984; Bogdanov,

Kolomiets, 2007). According to literature data, the formation of a sex body, which gradually moves into the nucleus periphery in prophase I of meiosis, is considered to be characteristic of mammalian males with heteromorphic XY sex chromosomes. In *E. tancrei* as in *E. talpinus*, XX chromosomes are isomorphic in the pattern of G-banding in females and males, and a sex body is also formed in representatives of these species (Bogdanov et al., 1986). Moreover, the sex bivalent of *E. talpinus* is surrounded with an electron-dense cloud, which is a morphological feature of silencing of sex chromosome genes of males (Homolka et al., 2007). In contrast to males, the behaviour and SC structure of the sex bivalent SC in females are identical to those of autosomes.

The distribution of SCP3, a major protein of the axial elements of chromosomes, in the asynaptic regions of XX chromosomes is powder-like, whereas in mice SCP3 not only contributes to thickening of the axial elements, but it is also a component of the protein coverlet involved in the process of inactivation of sex chromosomes and their isolation from autosomes (Turner et al., 2000). Condensation of X and Y chromosomes during formation of sex (XY) bodies is one of the cardinal characteristics distinguishing male from female meiosis in mammals. It is considered to be a morphological manifestation of inactivation of meiotic sex chromosomes, or MSCI (Forejt, 1984; Turner et al., 2000; Homolka et al., 2007).

During meiotic prophase I the structure and behaviour of the axial structures of the sex bivalent in oocytes were generally similar to those of autosomal bivalents. During prophase I of the male meiosis, XX chromosomes formed a closed sex bivalent and formed a typical sexual body. Thus, despite the isomorphism showed by G-banding of the XX sex chromosomes in males and females of *E.*

talpinus, we present evidence of a considerable dissimilarity in structure and behaviour of male and female sex and autosomal bivalents at prophase I of meiosis.

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